PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	James B. McCarthy et al.	Group Art Unit:	1642
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For: METHODS OF USE OF β1-INTEGRIN INHIBITORS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to taking up the above-identified application for examination, please amend the application as follows:

Please replace the paragraph beginning at page 35, line 2, with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to indicate the changes made.

Transient cerebral ischemia and associated brain injury may be mediated by several factors, including inflammatory processes (Hallenbeck et al., Stroke, 17, 246-253 (1986)). Leukocyte infiltration into ischemic tissue is a pathophysiological response, which often further aggravates ischemic injury by attenuating microvascular blood flow, and releasing chemical mediators such as free oxygen radicals (Kochanek et al., Stroke, 23, 1367-1379 (1992); and Matsuo et al., J. Cereb. Blood Flow Met., 15, 941-947 (1995)). Cell adhesion molecules play important roles in leukocyte-endothelial interactions: the selectins (Lasky, Science, 258, 964-969 (1992)), the integrins, and the immunoglobulin superfamilies (Springer, Nature, 346, 425-434 (1990)). Integrins which contain β_1 subunits usually are associated with mediating adhesion to extracellular matrix

constituents (Springer, Nature, 346, 425-434 (1990)) whereas β_2 integrins are largely involved in cell-cell interactions. One of these extracellular matrix macromolecules is fibronectin, which is found in plasma, cell matrix, and on the cell surface. These molecules can support leukocyte adhesion to endothelial cells (Akiyama et al., Adv. Enzymol., 59, 1-57 (1987)).

Please replace the paragraph beginning at page 35, line 18, with the following rewritten paragraph. Per 37 C.F.R. §1.121, this paragraph is also shown in Appendix A with notations to indicate the changes made.

Fibronectin possesses multiple domains recognized by integrins, including arginyl-glycyl-aspartic acid (RGD). The latter interacts selectively with α5β1 integrin, and the alternately spliced connecting segment domain (CS-1) which is recognized selectively by α4β1 integrin (Akiyama et al., Adv. Enzymol., 59, 1-57 (1987); and Guan et al., Cell, 60, 53-61 (1990)). Over the last few years several novel (nonRGD/nonCS-1) bioactive peptides from fibronectin that: a) antagonize leukocyte adhesion of activated lymphocytes and monocytes *in vitro* when used as soluble antagonists and b) show efficacy for improved outcomes in several *in vivo* animal models of chronic and acute inflammation when administered intravenously. These models include bacterial cell wall-induced arthritis in rats, models of autoimmune disease such as TGF-β -/- mice, and reperfusion injury in rat transient cerebral ischemia and in rabbit burn models (Hines et al., Proc. Natl. Acad. Sci., USA, 91, 5187-5191 (1994); Wahl et al., J. Clin. Invest., 94, 655-662 (1994); and unpublished data).